

REMARKS

Claims 1-42 were pending in the application. Claims 1, 14-15, 17-20, 22-23, 32-33, 35-38, and 41-42 have been amended and claims 16, 34, and 40 have been canceled without prejudice. Accordingly, upon entry of the amendments presented herein, claims 1-15, 17-33, 35-39, and 41-42 will remain pending in the application.

At paragraph 2 of the present Office Action, the Examiner has indicated that claims "1, 3, 4, 6, 9-21, 23, 25, 26, and 28-40 are under consideration and that all other claims are withdrawn from further consideration pursuant to 37 C.F.R. 1.142(b) as being drawn to a nonelected species." The Examiner has also objected to claims 1, 3, 4, 9-13, 15-21, 23 and 28 as allegedly reciting non-elected species. Applicants acknowledge the withdrawal of claims 2, 5, 7, 8, 22, 24, 27, and 41-42 and the Examiner's objection to the claims. In response to the restriction requirement set forth in the Office Action mailed February 16, 2006, Applicants elected the species of Mannitol for continued examination. However, as acknowledged by the Examiner, Applicants will be entitled to consideration of claims to additional species which are written in dependent form or otherwise include all the limitations of an allowed generic claim as provided by 37 C.F.R. § 1.141 *et seq.*

Support for the amendments to the claims may be found throughout the specification and the claims as originally filed. Specifically, support for the amendments to claims 1, 14-15, 17-20, 22-23, 33, 35-38, and 40-42 may be found at least, for example, at page 2, lines 6-17 and lines 26-31; page 3, lines 10-14; page 3, line 31 through page 4, line 16; page 5, lines 10-13; page 6, lines 23-30; page 10, lines 17-20; page 11, lines 7-31; page 13, lines 3-7; page 18, lines 9-12 and Example 6 of the specification.

No new matter has been added. Any amendment and/or cancellation of the claims should in no way be construed as an acquiescence to any of the Examiner's rejections and was performed solely in the interest of expediting prosecution of the application. Applicants reserve the right to pursue the claims as originally filed in this or a separate application(s).

***Rejection of Claims 1, 4, 9, 10, 12, 13, 15, 20, 21, 23, 26, 29-31, 33, and 38-40
Under 35 U.S.C. § 102(b)***

The Examiner has rejected claims 1, 4, 9, 10, 12, 13, 15, 20, 21, 23, 26, 29-31, 33, and 38-40 under 35 U.S.C. § 102(b) as being anticipated by Foster *et al.* (U.S. Patent No. 5,217,954). In particular, the Examiner is of the opinion that

Foster *et al.* teach preparation of a pharmaceutical formulation comprising a protein, bFGF, a stabilizing chelator, such as DTPA or EGTA. The formulation comprises optionally an agent for tonicity, a preservative or other auxiliaries, such as mannitol, glycerol, sodium chloride (see e.g., columns 3-6) or Tris (Example 1). The concentration of chelating agent is present in amounts of from about 0.0001% to about 2.0% (weight/weight) of the overall formulation (the 4th paragraph of column 4), which is within the recited concentration of DTPA, about 1 uM to about 10 mM in claim 4. Foster *et al* teach that the stabilizer can be used in combination with other stabilizers, such as citrate (the 2nd paragraph of column 5) and that the formulation can be prepared in a buffer system, such as sodium citrate (the 4th paragraph of column 5), with the pH of the formulation being from about 2 to about 8 (the 6th paragraph of column 5). Foster *et al.* teach continuous release formulations, including microcapsules that are essentially small particles of active compounds embedded in a suitable polymer (the 4th paragraph of column 5). Foster *et al.* further teach that the formulation comprises 0.01%-10% FGF in solution (lines 48-49 of column 6, and in Example 4, the concentration of FGF is 100 ug/ml.

Applicants respectfully traverse the Examiner's rejection for the following reasons.

As amended, claim 1, and claims depending therefrom, are directed to a composition comprising *an antibody, or fragment thereof*, formulated with DTPA and an agent selected from the group consisting of DEF, mannitol, methionine, and histidine, in an amount effective to protect the antibody or fragment thereof against oxidation. Claim 23, and claims depending therefrom, are directed to methods for preparing a stabilized protein composition, comprising formulating *an antibody, or fragment thereof*, together with DTPA and an agent selected from the group consisting of DEF, mannitol, methionine, and histidine, in an amount effective to protect the antibody or fragment thereof against oxidation.

For a prior art reference to anticipate a claimed invention under 35 U.S.C. § 102, the prior art must teach *each* and *every* element of the claimed invention. *Lewmar Marine v. Bariant*, 827 F.2d 744, 3 USPQ2d 1766 (Fed. Cir. 1987). Foster *et al.* teach pharmaceutical

formulations which “provide a stabilized basic fibroblast growth factor (bFGF) which is less susceptible to oxidation or metal-induced aggregation by including an amount of a chelating agent effective to stabilize the bFGF” and methods of preparing the same (see abstract). As acknowledged by the Examiner at page 5 of the present Office Action, Foster *et al.* do not teach a composition comprising *an antibody, or fragment thereof*, formulated with DTPA and an agent, nor do Foster *et al.* teach methods for preparing a stabilized protein composition, comprising *an antibody, or fragment thereof*, together with DTPA and an agent. Accordingly, since Foster *et al.* fail to teach or suggest *each and every* element of claims 1, 23, and claims depending therefrom, Applicants respectfully request that this section 102(b) rejection be reconsidered and withdrawn.

***Rejection of Claims 1, 3, 4, 6, 9-13, 15, 21, 23, 25, 26, 28-31, 33, 39, and 40
Under 35 U.S.C. § 102(b)***

The Examiner has also rejected claims 1, 3, 4, 6, 9-13, 15, 21, 23, 25, 26, 28-31, 33, 39, and 40 under 35 U.S.C. § 102(b) as being anticipated by Kerwin *et al.* (U.S. Patent No. 5,929,031). In particular, the Examiner is of the opinion that

Kerwin *et al.* teach a preparation of a pharmaceutical composition (column 8), which comprises a protein, hemoglobin at a concentration of 0.001% to 90% (w/v) (4 mg/ml and 100 mg/ml were used in Example 1 and 2), a reducing agent, such as sodium ascorbate or 0.03% (w/v) polysorbate 80 (lines 24-25 of column 13), chelators, such as 0-200 uM of DTPA and/or EGTA (lines 45-51 of column 8), 0-2 M of mannitol (lines 39-42 of column 8), which is within the range recited in claim 6. The formulation may also comprise one or more buffers, such as citrate or Tris (line 65 of column 12), and salts, such as sodium chloride (lines 32-35). The pH of the composition can be at about 6.5-9.5 (line 52 of column 8).

Applicants respectfully traverse the Examiner’s rejection for the following reasons. As discussed above, claim 1, and claims depending therefrom, are directed to a composition comprising *an antibody, or fragment thereof*, formulated with DTPA and an agent selected from the group consisting of DEF, mannitol, methionine, and histidine, in an amount effective to protect the antibody or fragment thereof against oxidation. Claim 23, and claims depending therefrom, are drawn to methods for preparing a stabilized protein composition, comprising formulating *an antibody, or fragment thereof*, together with DTPA and an agent selected from

the group consisting of DEF, mannitol, methionine, and histidine, in an amount effective to protect the antibody or fragment thereof against oxidation.

For a prior art reference to anticipate a claimed invention under 35 U.S.C. § 102, the prior art must teach *each* and *every* element of the claimed invention. *Lewmar Marine v. Bariant*, 827 F.2d 744, 3 USPQ2d 1766 (Fed. Cir. 1987). Kerwin *et al.* teach storage stable hemoglobin solutions and methods of preparing the same (see abstract). As acknowledged by the Examiner at page 6 of the present Office Action, Kerwin *et al.* do not teach a composition comprising *an antibody, or fragment thereof*, formulated with DTPA and an agent, nor do Kerwin *et al.* teach methods for preparing a stabilized protein composition, comprising *an antibody, or fragment thereof*, together with DTPA and an agent. Accordingly, since Kerwin *et al.* fail to teach or suggest *each* and *every* element of claims 1, 23, and claims depending therefrom, Applicants respectfully request that this section 102(b) rejection be reconsidered and withdrawn.

Rejection of Claims 16-19 and 34-37 Under 35 U.S.C. § 103(a)

The Examiner has rejected claims 16-19 and 34-37 under 35 U.S.C. § 103(a) as being obvious over Foster *et al.* (U.S. Patent No. 5,217,954), as applied to claims 1, 4, 9, 10, 12, 13, 15, 20, 21, 23, 26, 29-31, 33, and 38-40 and further in view of Hagiwara *et al.* (U.S. Patent No. 6,165467). The Examiner relies on Foster *et al.* for teaching “preparing a stabled formulation comprising FGF,” but acknowledges that “Foster et al. do not teach preparing a formulation comprising an antibody, a monoclonal antibody or a human antibody.” The Examiner relies on Hagiwara *et al.* for teaching the preparation of “a stable human monoclonal antibody preparation (see, e.g., Abstract)” and that human monoclonal antibodies have the undesirable property of easily aggregating and precipitating in a solution state. Based on the foregoing, the Examiner concludes that

it would have been obvious to one of skill in the art to prepare a pharmaceutical composition comprising a human monoclonal antibody instead of FGF according to the methods taught by Foster et al. with a reasonable expectation of success. One would have been motivated to do so because a human monoclonal antibody possesses characteristics that tend to form aggregates as taught by Hagiwara et al. (the 4th paragraph of column 1), and thus the formulation taught by Foster et al. would stabilize a human monoclonal antibody.

Applicants respectfully traverse the Examiner's assertion that the proposed combination of the above-cited references would have rendered the claimed invention obvious to the ordinarily skilled artisan at the time of the invention. Reconsideration and withdrawal of the rejection in light of the following discussion is respectfully requested.

To establish a *prima facie* case of obviousness, it is necessary for the Examiner to present evidence, preferably in the form of some teaching, suggestion, incentive or inference in the applied references, or in the form of generally available knowledge, that one having ordinary skill in the art would have been motivated to make the claimed invention and would have had a reasonable expectation of success in making the claimed invention. Under section 103, “[b]oth the suggestion and the expectation of success must be founded in the prior art, not in applicant's disclosure” (*Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd.* 927 F.2d 1200, 1207, 18 USPQ2d 1016 (Fed. Cir. 1991), quoting *In re Dow Chemical Co.*, 837 F.2d 469, 473, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988)). Moreover, when a combination of references are used to establish a *prima facie* case of obviousness, the Examiner must present evidence that one having ordinary skill in the art would have been motivated to combine the teachings in the applied references in the proposed manner to arrive at the claimed invention. See, e.g., *Carella v. Starlight Archery*, 804 F.2d 135, 231 USPQ 644 (Fed. Cir. 1986); and *Ashland Oil, Inc. v. Delta Resins and Refractories, Inc.*, 776 F.2d 281, 227 USPQ 657 (Fed. Cir. 1985).

Applying this standard to the references cited by the Examiner, it is clear that the Examiner has not met the burden of providing sufficient evidence to motivate a person of ordinary skill in the art to arrive at a composition comprising an antibody, or fragment thereof, formulated with DTPA and an agent selected from the group consisting of DEF, mannitol, methionine, and histidine, in an amount effective to protect the antibody, or fragment thereof, against oxidation or a method for preparing a stabilized protein composition, comprising formulating an antibody, or fragment thereof, together with DTPA and an agent selected from the group consisting of DEF, mannitol, methionine, and histidine, in an amount effective to protect the antibody or fragment thereof against oxidation.

Foster *et al.* teach formulations containing fibroblast growth factor (bFGF) and methods for preparing the same. Foster *et al.* also teach the use of mannitol as a ***bulking agent*** in order to formulate FGF as a topical vehicle formulation. Specifically, at column 5, lines 19-31, Foster *et al.* teach that

[f]or parenteral, for example, subcutaneous or intramuscular, or topical administration, ***bFGF formulations are converted into a solution, gel or emulsion, if desired, using the pharmaceutical substances customary for this purpose, such as solubilizers, thickening agents, emulsifiers, agents for tonicity, preservatives or other auxiliaries.*** Examples of suitable solvents for the new active compounds and the corresponding physiologically tolerated salts are: water, physiological saline solutions or alcohols, for example ethanol, propanediol, glycerol, or ***mannitol***, as well as sugar solutions, such as glucose or lactose solutions, or a mixture of the various solvents mentioned [***emphasis added***].

However, Foster *et al.* fail to teach or suggest that mannitol may be used to prevent oxidation of proteins, *e.g.*, antibodies.

The secondary reference of Hagiwara *et al.* does not make up for the aforementioned deficiencies in the primary reference of Foster *et al.* Specifically, Hagiwara *et al.* teach “a stabilized human monoclonal antibody preparation containing mannitol” (see abstract). However, the mannitol taught in Hagiwara *et al.* is used as a ***bulking agent*** in order to permit lyophilization (see, for example, column 1, lines 30-58 of Hagiwara *et al.*). Similar to the situation in Foster *et al.*, the mannitol in Hagiwara *et al.* prevents aggregation of the protein. There is no teaching or suggestion in Hagiwara *et al.* with respect to the use of mannitol in preventing oxidation of antibodies. Nor is there any teaching or suggestion in Hagiwara *et al.* with respect to compositions comprising DTPA and an agent, such as mannitol, in an amount effective to prevent oxidation of proteins. Thus, there is no motivation to combine the teachings of Foster *et al.* and Hagiwara *et al.* since Hagiwara *et al.* teaches a use of mannitol for a purpose unrelated to the problem solved by the present invention, *i.e.*, protecting antibodies against oxidative degradation.

In summary, neither Foster *et al.* nor Hagiwara *et al.*, alone or in combination, teach a composition comprising an antibody, or fragment thereof, formulated with DTPA and an agent selected from the group consisting of DEF, mannitol, methionine, and histidine, in an amount effective to protect the antibody, or fragment thereof, against oxidation or a method for preparing a stabilized protein composition, comprising formulating an antibody, or fragment thereof, together with DTPA and an agent selected from the group consisting of DEF, mannitol, methionine, and histidine, in an amount effective to protect the antibody or fragment thereof against oxidation, as required by the pending claims. Furthermore, there is no motivation to combine the teachings of the references cited by the Examiner to arrive at the present invention. Accordingly, Applicants respectfully submit that based on the cited references, the Examiner has failed to establish a *prima facie* case of obviousness and request that this section 103 rejection be reconsidered and withdrawn.

Rejection of Claims 14 and 32 Under 35 U.S.C. § 103(a)

The Examiner has also rejected claims 14 and 32 under 35 U.S.C. § 103(a) as being unpatentable over Kerwin *et al.* (U.S. Patent No. 5,929,031), as applied to claims 1, 3, 4, 6, 9-13, 15, 21, 23, 25, 26, 28-31, 33, 39, and 40 above, and further in view of Hagiwara *et al.* (U.S. Patent No. 6,165467). The Examiner relies on Kerwin *et al.* for teaching “preparing a stabled formulation comprising hemoglobin,” but acknowledges that “Kerwin et al. do not teach preparing a formulation comprising an antibody, a monoclonal antibody or a human antibody.” As discussed above, the Examiner relies on Hagiwara *et al.* for teaching “preparing a stable human monoclonal antibody preparation (see, e.g., Abstract)” and that human monoclonal antibodies have the undesirable property of easily aggregating and precipitating in a solution state. Based on the foregoing, the Examiner concludes that

it would have been obvious to one of skill in the art to prepare a pharmaceutical composition comprising a human monoclonal antibody instead of hemoglobin according to the methods taught by Kerwin et al. with a reasonable expectation of success. One would have been motivated to do so because a human monoclonal antibody and a protein have the basic components – amino acids and a human monoclonal antibody possesses characteristics that tend to form aggregates as

taught by Hagiwara et al. (the 4th paragraph of column 1), and thus the formulation taught by Kerwin et al would stabilize a human monoclonal antibody.

Applicants respectfully traverse the Examiner's assertion that the proposed combination of the above-cited references would have rendered the claimed invention obvious to the ordinarily skilled artisan at the time of the invention. Reconsideration and withdrawal of the rejection in light of the following discussion is respectfully requested.

As discussed above, to establish a *prima facie* case of obviousness, it is necessary for the Examiner to present evidence, preferably in the form of some teaching, suggestion, incentive or inference in the applied references, or in the form of generally available knowledge, that one having ordinary skill in the art would have been motivated to make the claimed invention and would have had a reasonable expectation of success in making the claimed invention. Under section 103, “[b]oth the suggestion and the expectation of success must be founded in the prior art, not in applicant's disclosure” (*Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd.* 927 F.2d 1200, 1207, 18 USPQ2d 1016 (Fed. Cir. 1991), quoting *In re Dow Chemical Co.*, 837 F.2d 469, 473, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988)). Moreover, when a combination of references are used to establish a *prima facie* case of obviousness, the Examiner must present evidence that one having ordinary skill in the art would have been motivated to combine the teachings in the applied references in the proposed manner to arrive at the claimed invention. See, e.g., *Carella v. Starlight Archery*, 804 F.2d 135, 231 USPQ 644 (Fed. Cir. 1986); and *Ashland Oil, Inc. v. Delta Resins and Refractories, Inc.*, 776 F.2d 281, 227 USPQ 657 (Fed. Cir. 1985).

Applying this standard to the references cited by the Examiner, it is clear that the Examiner has failed to meet the burden of providing evidence to motivate a person of ordinary skill in the art to arrive at a composition comprising an antibody, or fragment thereof, formulated with DTPA and an agent selected from the group consisting of DEF, mannitol, methionine, and histidine, in an amount effective to protect the antibody, or fragment thereof, against oxidation or a method for preparing a stabilized protein composition, comprising formulating an antibody, or fragment thereof, together with DTPA and an agent selected from the group consisting of

DEF, mannitol, methionine, and histidine, in an amount effective to protect the antibody or fragment thereof against oxidation.

Kerwin *et al.* teach stable hemoglobin solutions which may contain one or more chelating agents (such as DTPA) and one or more carbohydrates (such as mannitol). Specifically, at column 8, lines 38-51, Kerwin *et al.* teach that

the compositions of the invention can include 0-2 M of one or more carbohydrates (for example, reducing carbohydrates such as glucose, maltose, lactose or non-reducing carbohydrates such as sucrose, trehalose, raffinose, mannitol, isosucrose or stachyose) and 0-2 M of one or more alcohols or poly alcohols (such as polyethylene glycols, propylene glycols, dextrans, or polyols). The compositions of the invention can also contain 0.005-1% of one or more surfactants and 0-200 μ M of one or more chelating agents (for example, ethylenediamine tetraacetic acid (EDTA), ethylene glycol-bis (β -aminoethyl ether) N,N,N',N'-tetraacetic acid (EGTA), ophenanthroline, diethylamine triamine pentaacetic acid (DTPA also known as pentaacetic acid) and the like).

In contrast to the present invention, however, Kerwin *et al.* fail to teach or suggest that mannitol can be used to prevent oxidation of antibodies.

The secondary reference of Hagiwara *et al.* does not make up for the aforementioned deficiencies in the primary reference of Kerwin *et al.* Specifically, Hagiwara *et al.* teach “a stabilized human monoclonal antibody preparation containing mannitol” (see abstract). As indicated above, the mannitol taught in Hagiwara *et al.* is used as a **bulking agent** in order to permit lyophilization (see, for example, column 1, lines 30-58 of Hagiwara *et al.*). Similar to the situation in Kerwin *et al.*, the mannitol in Hagiwara *et al.* prevents aggregation of the protein. There is no teaching or suggestion in Hagiwara *et al.* with respect to the use of mannitol in preventing oxidation of antibodies. Nor is there any teaching or suggestion in Hagiwara *et al.* with respect to compositions comprising DTPA and an agent, such as mannitol, in an amount effective to prevent oxidation of proteins. Thus, there is no motivation to combine the teachings of Kerwin *et al.* and Hagiwara *et al.* since Hagiwara *et al.* teaches a use of mannitol for a

purpose unrelated to the problem solved by the present invention, *i.e.*, protecting antibodies against oxidative degradation.

In summary, neither Kerwin *et al.* nor Hagiwara *et al.*, alone or in combination, teach a composition comprising an antibody, or fragment thereof, formulated with DTPA and an agent selected from the group consisting of DEF, mannitol, methionine, and histidine, in an amount effective to protect the antibody, or fragment thereof, against oxidation or a method for preparing a stabilized protein composition, comprising formulating an antibody, or fragment thereof, together with DTPA and an agent selected from the group consisting of DEF, mannitol, methionine, and histidine, in an amount effective to protect the antibody or fragment thereof against oxidation, as required by the pending claims. Furthermore, there is no motivation to combine the teachings of the references cited by the Examiner to arrive at the present invention. Accordingly, Applicants respectfully submit that based on the cited references, the Examiner has failed to establish a *prima facie* case of obviousness and request that this section 103 rejection be reconsidered and withdrawn.

CONCLUSION

In view of the above amendments and remarks set forth above, it is respectfully submitted that this application is in condition for allowance. If there are any remaining issues or the Examiner believes that a telephone conversation with Applicants' Attorney could be helpful in expediting prosecution of this application, the Examiner is invited to call the undersigned at (617) 227-7400.

Dated: July 28, 2006

Respectfully submitted,

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